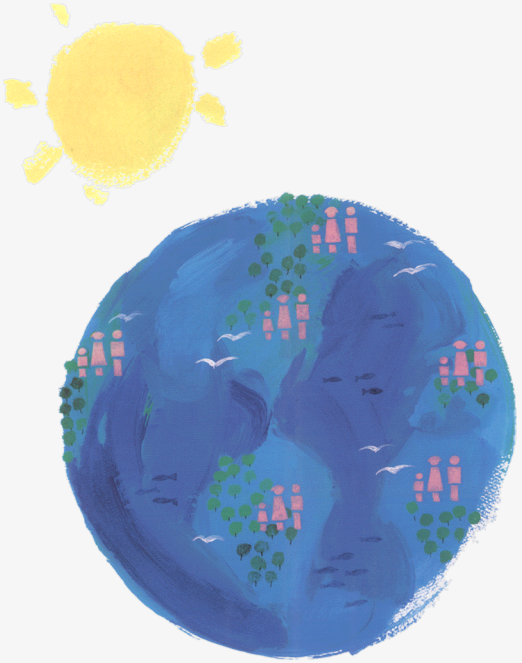
NICEATM

National Toxicology Program
Interagency Center for the Evaluation of Alternative Toxicological Methods

ICCVAM

Interagency Coordinating Committee on the Validation of Alternative Methods



ICCVAM Nominations

Raymond Tice, Ph.D.
Deputy Director, NICEATM

SACATM Meeting
Bethesda, MD
June 12, 2006

National Toxicology Program

NIEHS

National Institutes of Health

Department of Health & Human Services • USA

ICCVAM Nomination and Submission Process

NICEATM (http://iccvam.niehs.nih.gov)
- Solicits, receives, and tracks submissions and nominations
- Conducts preliminary evaluation of each submission or nomination
  - determines completeness of each submission or nomination
  - summarizes findings
  - proposes appropriate future efforts (e.g., workshop, expert panel meeting, peer review meeting, expedited review, validation study)

↓

ICCVAM
- Reviews NICEATM preliminary evaluation report
- Develops draft recommendations on priority for future efforts
- Seeks comment from the public on the nominated or submitted test method (via NICEATM)

↓

SACATM
- Considers public comments on the nominated or submitted test method
- Comments on NICEATM and ICCVAM draft recommendations (activities and priorities)

↓

ICCVAM
- Considers SACATM and public comments
- Finalizes recommendations and priorities
- NICEATM estimates resource requirements

↓

Director, ETP/NIEHS
- Responds to NICEATM resource requests for proposed test method activities

↓

Director, NICEATM
- Informs ICCVAM of availability of resources for activities recommended for nominated or submitted test methods
- If appropriate, ICCVAM Working Group established
- If appropriate, test method evaluations or validation studies organized in conjunction with ICCVAM Working Group

* ICCVAM (2003) *ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods*. NIH Publication No. 03-4508, 50 pp. Research Triangle Park, NC, USA.

ICCVAM Criteria for Nomination Priority Setting

1. The extent to which the proposed test method is:
   - Applicable to regulatory testing needs
   - Applicable to multiple agencies/program
2. The extent of expected use or application and impact on human, animal, or ecological health.
3. The potential for the test method, compared to current methods, to:
   - Refine animal use (i.e., decrease or eliminate pain and distress)
   - Reduce animal use
   - Replace animal use
4. The potential for the test method to provide improved prediction of an adverse health or environmental effect, compared to current methods.
5. The extent to which the test method provides other advantages, such as reduced cost and time to perform, compared to current methods.

Murine Local Lymph Node Assay (LLNA)

- Skin sensitizers induce lymphocyte proliferation in the lymph nodes that drain at the site of application.
- Measurement of the increase in lymphocyte proliferation (vs. control) is used in the LLNA to identify chemical sensitizers.
- Test method originally reviewed by ICCVAM in 1998.
  - The Peer Panel Review consensus was that the LLNA was sufficiently validated as a stand-alone alternative to the guinea pig skin sensitization test methods for the identification of skin sensitizers, with identified limitations.
- Based on the ICCVAM evaluation and recommendations, the LLNA protocol was incorporated into national and international test guidelines for the assessment of skin sensitization.
  - e.g., EPA Health Effects Testing Guidelines on Skin Sensitization.
  - OECD adopted testing guidelines (TG 429) that were based on the ICCVAM-recommended protocol from this evaluation.

ICCVAM Nomination

- Nomination received January 10, 2007 from the CPSC for the evaluation of the validation status of the following:
  - LLNA as a stand-alone assay for potency determinations (including severity) for classification purposes
  - Non-radioactive LLNA protocols
  - The LLNA “cut-down” or “limit” test
  - Use of LLNA to test mixtures, aqueous solutions, and metals
  - Current applicability domain for the LLNA

Recommended Priority is “High” (1)

1. The extent to which the proposed test method is applicable to regulatory testing needs.
   - The proposed modifications of the LLNA are applicable to the regulatory testing needs for several agencies (e.g., CPSC, EPA, FDA)
2. The extent of expected use or application and impact on human, animal, or ecological health
   - Regulatory testing needs require the assessment of skin sensitization hazard for labeling purposes. The proposed modifications to the LLNA could be applied to these testing needs.
3. The potential for the method, compared to current methods, to refine, reduce, and replace animal use
   - Just as the traditional LLNA, all of the nominated activities have the potential to reduce and refine animal use when compared to the Guinea pig methods.
   - The proposed limit test could further reduce the use of animals (but not applicable if potency categorization is required in future testing)

Recommended Priority is “High” (2)

3. The potential for the method to provide improved prediction of an adverse health or environmental effect, compared to current methods
   - There is the potential for the LLNA to be used to estimate potency.
4. The extent to which the test method provides other advantages, such as reduced cost and time to perform, compared to current methods
   - Non-radioactive methods would expand the use of the LLNA for skin sensitization to laboratories where the use of radioactive-based test methods is prohibited.
   - Compared to Guinea pig test methods, the LLNA reduces the required testing time.

Proposed NICEATM and IWG Activities (1)

- Publish a *Federal Register (FR)* notice requesting:
  - Public comments on the appropriateness and relative priority of ICCVAM proposed activities, including
    - Preparing Background Review Documents (BRDs)
    - Developing performance standards
    - Convening an expert panel to review the nominated methods
  - Nomination of expert scientists for consideration as members for a potential Panel
  - Submission of data from the traditional and/or modified versions of the LLNA
  - Publication date was May 17, 2007; comments due by June 15, 2007
- Search for relevant data
  - Additional literature searches
  - Contact interested stakeholders for available data and information

Proposed NICEATM and IWG Activities (2)

- Expand the 1998 database of test substances and results and re-evaluate LLNA performance compared to Guinea pig test methods and human response data.
- Prepare draft BRDs that provides a comprehensive review of the validation status of:
  - LLNA as a stand-alone assay for potency determinations for classification purposes (using UN GHS proposed criteria)
  - Non-radioactive LLNA protocols
  - The LLNA limit test
  - The current applicability domain, to include the use of LLNA to test mixtures, aqueous solutions, and metals

Proposed NICEATM and IWG Activities (3)

- Prepare proposed draft ICCVAM test method recommendations for:
  - Current uses and limitations for these methods
  - Test method protocols and/or decision criteria
  - Performance standards
  - Future/additional studies
- Convene an expert panel to review draft BRDs and draft recommendations

Proposed Timeline

May 17	*FR* notice: request for data, expert nominations
June 12	SACATM meeting to comment on priority for LLNA review activities
June 15	Comments in response to the *FR* notice due
June 27	ICCVAM considers public and SACATM comments in establishing final priority
April-Sept?	IWG and NICEATM develop draft BRDs and draft test method recommendations in conjunction with ECVAM and JaCVAM
Sept?	Obtain ICCVAM endorsement of draft BRDs and draft test method recommendations for public release
October?	Release draft BRDs and draft test method recommendations to expert panel and to the public for comment
Feb 2008?	Convene Peer Review Panel Meeting

Public Comments Received

- Three comments received to date
  - http://iccvam.niehs.nih.gov/methods/immunotox/immunotox.htm
- Comments provide:
  - Support for the nominated activities
  - Offers of data for use in the evaluations
  - Nominations of experts for consideration as members of the peer review panel.

Discussion Questions for SACATM

(Lead Discussants: Drs. Cunningham, Ehrich, Diggs)

1. Do you have any comments on the CPSC's nomination of the LLNA? Specifically, that ICCVAM assess the validation status of:
   a. The LLNA as a stand-alone test for determining potency (including severity) for the purpose of classifying hazards.
   b. Modifications to the LLNA protocol that use non-radioactive methods to determine lymphocyte stimulation in the draining lymph nodes.
   c. The LLNA "cut-down" or "limit dose" procedure.
   d. The ability of the LLNA to test mixtures, aqueous solutions, and metals.
   e. The current chemical applicability domain of the LLNA.
2. Do you agree with ICCVAM's preliminary assessment and recommendations for this nomination? If no, please explain.